Medical Information

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An A,B,C,D of Cancer Chemotherapy

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ONE OF THE major highlights in the management of metastatic cancer during the last few years has been the development of four new chemotherapy drugs. Their addition to the therapeutic armamentarium of chemotherapists who treat patients with cancer has led to palliation and rates of complete and partial tumor regression never before possible. However, such agents should be used only by physicians familiar with the drugs and their toxicities. The following will emphasize important features of these four agents, referred to as the *A,B,C,D* of new cancer chemotherapy (Table 1).

The *A* of this group refers to doxorubicin hydrochloride (Adriamycin),[1] an antibiotic of the anthracycline group isolated from a culture of Streptomyces organisms and developed in Italy. Currently marketed in the United States by Adria Laboratories Inc., it is an analogue of daunomycin, a drug supplied by the National Cancer Institute, which is helpful in the management of acute leukemia in adults.

Adriamycin appears to exert its antitumor activity by binding to DNA through intercalation between base pairs, and by inhibiting RNA synthesis by means of steric hindrance and template disordering. There is extensive tissue binding by this drug, and it is metabolized predominantly by the liver. Prolonged plasma levels, therefore, are associated with exaggerated clinical toxicity. The usual dosage is 40 to 60 mg per sq meter of body surface area* given intravenously every three to four weeks.

Adriamycin is a red powder packaged in 10 mg and 50 mg vials. It is an expensive drug, with the current average cost of $16 and $74 for 10 mg and 50 mg vials, respectively. The drug should be reconstituted with sterile water or saline solution. Such solution is stable for 24 hours at room temperature and for at least 48 hours when kept in the refrigerator. Adriamycin as a powder is stable at room temperature.

The drug should be administered into a freely running intravenous infusion line in which the flow is 5 percent dextrose or normal saline solution, or both. Correct infusion technique is mandatory because extravasation of this drug is not only painful, but leads to massive tissue necrosis and slough. Adriamycin is incompatible with heparin and methotrexate, forming a precipitate with either of these medications.

The spectrum of activity against metastatic cancer is notable with this drug. Adriamycin, when combined with cyclophosphamide or other drugs effective in treatment of cancer of the breast, has produced complete and partial remission rates that are among the highest ever achieved.[2] It is also an agent of choice for patients with metastatic carcinoma of the thyroid and the bladder.[1]

Adriamycin has been incorporated into virtually every treatment program for the management of sarcoma. Indeed, its response rate has been so impressive that it is incorporated into adjuvant programs for the prevention of recurrent osteogenic sarcoma. It is noteworthy that the best response rates in sarcoma patients have been obtained when adriamycin has been combined in a program with dacarbazine,[3] one of the new drugs to be discussed later.

Adriamycin has shown significant activity in the management of Hodgkin disease refractory to conventional therapy with a combination of mechlorethamine, vincristine (Oncovin), procarbazine and prednisone (MOPP).[4] Studies now suggest that when combined with bleomycin, vinblastine and dacarbazine, it produces initial response rates as first-line therapy fully equal to that of MOPP. Adriamycin is also active in the management of malignant lymphomas in both the nodular and diffuse categories.[5]

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*Body surface area expressed in square meters can be easily calculated from standard nomograms using a patient's weight and height.

The drug has also been used successfully in combination therapy for bronchogenic carcinoma in virtually every cell type.[16] Recent studies have clearly indicated that it is notably active in the management of ovarian[6] and prostatic carcinoma.[7] Again, recent evidence suggests that it is at least equal to, if not superior to, daunomycin as the initial therapy for acute myelogenous leukemia.[8]

The toxicity of this drug is striking. It produces significant nausea and vomiting in more than 70 percent of patients, and alopecia will develop in almost all cases. The loss of hair is usually not permanent and regrowth may occur even while the patient is still receiving it. In some cases both texture and color of the hair may be altered with regrowth.

Stomatitis can be a dangerous complication and must be anticipated. As with almost all chemotherapeutic drugs, myelosuppression can be severe and affects both leukocytes and platelets. As mentioned above, one must be extremely careful to avoid local extravasation of the drug because necrosis of tissue may develop. The patient should also be warned that urine may turn red within a day after drug administration. This has no pathological significance.

Cardiomyopathy is a unique feature of the toxicity of Adriamycin.[9] Results of studies have indicated that this drug causes necrosis and changes in the myocardium beginning with a total dose as low as 240 mg per sq meter of body surface area. Results of follow-up studies of patients in whom Adriamycin therapy was discontinued indicate that such damage may continue for as long as a year after administration of the drug has been stopped. The predominant clinical manifestation has been congestive heart failure which may appear suddenly and, in many cases, has been refractory to conventional therapy. In some cases death has ensued. Electrocardio-

TABLE 1.—*Features of the A,B,C,D Chemotherapy*

Adriamycin	*Bleomycin*	*Nitrosoureas*	*DTIC*
MAJOR INDICATIONS IN VARIOUS TYPES OF CANCER PERCENT RESPONSES AS SINGLE AGENT* OR (IN COMBINATION)			
Breast 35-40* (60-70)	Head and neck . 30*	Brain 45*	Metastatic melanoma 25*
Thyroid 35*	Cervix 10*	Bronchogenic ... (30-60)	Hodgkin disease .. (90)
Bladder 35*	Hodgkin disease . (90)	Metastatic melanoma .... (20)	Soft tissue sarcoma (40)
Bronchogenic	Malignant	Hodgkin disease . (90)	
oat cell 30* (60-70)	lymphoma ... (40-60)		
non-oat cell 20* (30-40)			
Soft tissue sarcoma . (40)	Testicular .....(75-100)		
Osteogenic sarcoma . (20)			
Acute myelogenous leukemia ..... (40-60)			
Hodgkin disease ... (90)			
Malignant lymphoma (40-60)			
Ovary ..... (30-40)			
Prostate 25*			
HOW SUPPLIED AND APPROXIMATE COST			
10 mg vial $16	15 mg vial $40	Box containing 2 each of CCNU of 10, 40 and 100 mg capsule $14	100 mg vial $25
50 mg vial $74		BCNU 100 mg $15	200 mg vial $43
UNUSUAL TOXICITIES			
Cardiotoxicity; 100 percent alopecia	Pulmonary and dermatologic	Delayed myelosuppression	Severe nausea and vomiting

DTIC = Dimethyl triazeno imidazole carboxamide
CCNU = 1-(2-choloroethyl)-3-cyclohexyl-1-nitrosourea
BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea.

graphic rhythm abnormalities are common, most of which are nonspecific and correlate poorly with endomyocardial biopsy findings.[10]

Recently systolic time interval, the ratio of preejection period to left ventricular ejection time has been hailed by some as the most sensitive noninvasive test for predicting toxicity.[10]

Data from many sources indicate that the frequency of this problem rises notably when the total dose of Adriamycin equals or exceeds 550 mg per sq meter. Therefore, the current recommendation is that, except under exceptional circumstances, patients should not receive more than this amount of the drug. Furthermore, if radiation therapy has been given before in the mediastinum in patients older than 70, the dosage at which cardiomyopathy develops is much lower, and current recommendations call for discontinuing the drug at a cumulative dose of 450 mg per sq meter. It is interesting that children appear to tolerate higher dosages of the drug.

It has now been verified that Adriamycin is capable of producing a recall phenomenon, for example, severe skin reactions in areas previously treated with radiation. This can necessitate discontinuing the medication. Because Adriamycin is detoxified by the liver, toxicity is enhanced if full doses are administered when there is evidence of dysfunction of the liver. Therefore, half of the usual dose is recommended when the serum bilirubin level is greater than 1.5 mg per dl.

The *B* of the new chemotherapy drugs is bleomycin,[10] with the trade name Blenoxane, from Bristol Laboratories. This drug was developed in Japan and represents a mixture of antibiotics isolated from a strain of Streptomyces organisms. It binds DNA and causes inhibition of thymidine incorporation into DNA. It is unique among antitumor agents in that leukopenia and thrombocytopenia are rarely seen even with high doses.

Bleomycin is prepared as a sterile powder that can be reconstituted with 5 percent dextrose and normal saline solution or sterile water. Each ampule contains 15 units (mg) of bleomycin and is usually reconstituted with 2 to 5 ml of solution. The powder form is stable for at least two years at room temperature. There is no loss of biological activity when reconstituted solutions are refrigerated for four weeks in sterile rubber-stopped containers. Current cost of the drug is approximately $40 per 15 unit ampule.

Bleomycin can be given intravenously or intramuscularly. The latter method is associated with some brief burning pain, and a small volume must be used in order to prevent the development of sterile abscess. The usual dosage is 5 to 15 units per sq meter of body surface area administered once or twice a week.

The most common toxicity of the drug is related to the skin and mucous membrane surfaces. Mouth ulcers, rashes or hyperpigmentation of the skin may develop. Hyperkeratosis may develop at the tips of fingers and may be associated with significant pain and ulceration. In some patients this has led to gangrene. Alopecia may develop with prolonged use of the medication. Most of the skin problems gradually disappear after treatment is stopped.

Acute toxicity, usually developing within three to five hours after the injection, may be a problem and is associated with fever, chills, nausea and vomiting. If acute toxicity develops at all, it usually appears after the first dose. Treatment includes aspirin or antihistamines. Severe anaphylaxis has occasionally occurred and causes hypotension, mental confusion, fever, chills and wheezing. This is seen predominantly in patients with lymphoma; such patients should receive a test dose of one to two units of the drug when they are first treated.

Bleomycin also has a unique toxicity that limits the total dose that should be administered lest pulmonary interstitial fibrosis with severe and irreversible respiratory incapacity be produced.[11] Pathologic studies in such cases have shown prominent squamous metaplasia of the lining cells of the alveoli with prominent interstitial edema as well. This has been noted especially in patients with lymphoma, in whom x-ray films show diffuse interstitial infiltrates that may develop rapidly while the patient continues receiving therapy. Consequently, therapy with bleomycin should be followed carefully with pulmonary function tests if necessary, and physicians should not administer a total dose in excess of 250 mg per sq meter of body surface area. In patients older than 70 there is a greater chance of the problem developing and the drug must be used with extreme care.

Bleomycin has shown significant palliative activity in patients with squamous cell carcinoma, especially of the head and neck,[10] and of the cervix.[6] Unfortunately, the responses have been short-lived, rarely exceeding three months. Current research indicates that bleomycin works quite well when combined with other drugs in the treatment of cancer of the head and neck.[12] It has also

been shown to be effective, as noted earlier, when combined with other drugs in the therapy of Hodgkin disease and malignant lymphoma.[4] It has become an important component in combination drug therapy for testicular malignancies of all varieties.[13,14] Bleomycin has lent itself to a variety of drug combination programs because of its unique minimal toxicity in bone marrow.

The next new class of drugs is represented by the nitrosourea group, developed in the United States at the National Cancer Institute. The first member of this family that became commercially available, the *C* of the title, is CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea). This is now available as CeeNU, or lomustine, from Bristol Laboratories. Boxes containing two each of the 10, 40 and 100 mg capsules are currently priced at $14 each. The other drugs in the family are BCNU (1,3-bis(2-choroethyl)-1-nitrosourea) commercially available as BiCNU or carmustine in packages containing a vial of 100 mg of powder and a vial of 3 ml of diluent for $15 (also from Bristol Laboratories), and methyl-CCNU, supplied in capsules solely by the National Cancer Institute.

All three drugs are believed to alkylate with DNA and RNA. They have also been shown to inhibit certain enzymes through carbamylation of amino acids in proteins. All are administered in intermittent single dose schedules, although several are incorporated at present into multidrug regimens. CCNU and methyl-CCNU are given orally, whereas BCNU can be reconstituted with the supplied diluent (absolute ethanol) plus additional 27 ml of sterile water for intravenous injection. Unopened vials of BCNU must be refrigerated at about 4°C, and after reconstitution the drug will slowly decompose if kept at room temperature.

A unique aspect of these drugs is high lipid solubility and the relative lack of ionization at a physiological pH. This apparently allows the drugs to cross the blood-brain barrier effectively. There are no unusual antagonistic effects when combined with other anticancer agents.

Effects of toxicity include nausea and vomiting, predictable two to six hours after administration of any of the three drugs and usually lasting less than 24 hours. The toxicity is not dose limiting and is centrally mediated. Therefore, administration of antiemetic agents is usually begun at the time of, or just before, administration of the drug and is continued for 24 hours. The oral medications should be taken on an empty stomach at bedtime. It has been found that phenothiazine derivatives and other strong sedatives given before such medication will often help patients rest through the night without nausea and vomiting.

Thrombocytopenia occurs (to a level of 80,000 to 100,000 per cu mm) about four weeks after a dose and lasts one to two weeks. Leukopenia occurs about six weeks after a dose and lasts an additional week or two. Therefore, the unique feature of these drugs is that the effect in bone marrow is delayed, dose related, dose limiting and cumulative. Therefore, the drugs should be given at intervals of six to eight weeks. Previous radiotherapy or chemotherapy, or both, or infiltration of cancer cells in bone marrow, increases toxicity in the marrow and lower doses of the drugs should be administered.

Reports from the Brain Tumor Study Group have indicated that the use of BCNU, when combined with radiation therapy, has improved response rates in primary neoplasms of the brain.[16] The response rate in metastatic carcinoma has not been so notable. Apparently, the ability to cross the blood-brain barrier renders the drug first-line therapy for brain tumors. All three members of this new class of drugs have been shown to be effective in the treatment of advanced Hodgkin disease, including cases refractory to more conventional modes of therapy.[4]

Numerous reports appearing in the literature indicate that CCNU has become a valuable addition to effective therapy for carcinoma of the lung, especially oat cell carcinoma and adenocarcinoma.[17] The nitrosourea drugs have been effective in the treatment of malignant melanoma,[18] although they are not as effective as dacarbazine, the last drug to be discussed. Earlier studies have indicated that methyl-CCNU, when combined with 5-fluorouracil, produced the highest palliative responses yet obtained in the management of metastatic malignancy of the gastrointestinal tract. However, since then this view has been challenged and now it is clear that increased survival has not been achieved.[19] Studies have also indicated notable activity of these drugs in the treatment of multiple myeloma.[20]

With all three agents, blood counts should be checked before each dose and during the third to sixth week after initiation of therapy. Then decisions regarding subsequent dosage can be made and the doses can be reduced if necessary, or the interval between treatments can be increased. Other infrequent side effects include stomatitis, alopecia, mild anemia, anorexia and

increased liver function abnormalities. These drugs have also been described as producing disorientation, lethargy and dysarthria. Reconstituted BCNU solution should be administered through intravenous drip longer than one to two hours because there is burning, redness and occasional phlebitis at the injection site if the solution is given over shorter periods of time.

The fourth drug is DTIC (dimethyl triazeno imidazole carboxamide).[21] It was also developed at the National Cancer Institute and is marketed in powder form as dacarbazine, or DTIC-Dome, by Dome Laboratories. The action has not been clearly defined; possibilities include inhibition of DNA synthesis, interaction with the sulfhydryl group or acting as an alkylating agent. Results of studies show that dacarbazine is now the drug of choice for treating metastatic melanoma, where a clinical response of greater than 20 percent, has been achieved, and obtained remissions may last a long time.[21] As mentioned earlier, when incorporated with the drugs recently introduced for the treatment of Hodgkin Disease, DTIC produces response rates comparable to the standard MOPP regimen.[4] It is also an important component in combination therapy for sarcoma.[3]

Dacarbazine is packaged in 100 and 200 mg vials at a current cost of $25 and $43 per 12 bottles, respectively. The drug is reconstituted with sterile water and both must be kept refrigerated because the solution is stable for no more than eight hours at room temperature. The usual dosage has been 250 mg per sq meter of body surface area administered intravenously in less than a half hour on five consecutive days every three to four weeks. Some recent treatment protocols also call for administering the drug in a single dose of 600 to 900 mg per sq meter of body surface area every three to four weeks,[22] although documentation of comparable efficaciousness is lacking.

Invariably, there is severe burning pain along the infused vein. Nausea and vomiting are extremely severe. If the drug is given in a five-day course, nausea and vomiting are especially prominent on the first day or two, and then decrease on the subsequent days of administration. It is advisable to give the patient an ample supply of antiemetic agents during and immediately after administration of the drug. Occasionally, an influenza-like syndrome may appear even weeks after a large dose. Rarely, hypersensitivity reactions have been reported. There has been suppression mainly of leukocytes and platelets in bone marrow.

In summary, the development of the *A,B,C,D* drugs represents a major advance in the treatment of neoplastic disease. However, in view of the numerous unusual toxicities, it is critical that physicians become familiar with these drugs and understand the necessary precautions in using them.

Summary

Four antineoplastic agents recently introduced —Adriamycin *(A)*, bleomycin *(B)*, CCNU *(C)* and DTIC *(D)*—are discussed with regard to unique toxicities, modes of action, administration, cost and types of neoplasms in which the drugs are most effective. It is hoped that this will serve as a guide for practitioners in their daily care of patients with cancer.

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Medical Information

Vulnerability to Disulfiram Psychosis

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ABBREVIATIONS USED IN TEXT

DA = dopamine
DBH = dopamine-beta-hydroxylase
NE = norepinephrine

DISULFIRAM (Antabuse) is a drug commonly used in the management of impulsive drinking in patients addicted to alcohol. Besides the severe cardiovasular effects it produces with alcohol intake (by increasing circulating acetaldehyde levels through inhibition of the enzyme aldehyde dehydrogenase), disulfiram has various adverse effects when used alone. These effects include drowsiness, fatigue, impotence, headaches, skin eruptions and polyneuritis, as well as, most seriously, neurological toxicity and psychosis. Disulfiram delirium is probably mediated by toxic metabolites, such as carbon disulfide (CS_2).[1] Nontoxic psychosis produced by disulfiram is frequently missed in clinical practice, as evidenced by the continued use of disulfiram in affected patients, or a diagnosis of psychosis that disregards the role of disulfiram in its precipitation.

In this paper, a hypothesis of vulnerability to disulfiram psychosis is proposed, based on the current lines of evidence for the biological mechanisms involved in the psychoses.

The Dopamine Hypothesis

The dopamine (DA) hypothesis of schizophrenia[2] states that an increase in DA activity in certain brain areas (probably the mesolimbic and mesocortical tracts) is associated with psychotic symptoms in schizophrenic patients. According to this hypothesis, drugs that increase DA activity (that is, DA agonists) would worsen the symptoms of schizophrenia, and this has been confirmed with controlled studies using amphetamine and methylphenidate (DA agonists) as well as L-dopa (a DA precursor). These drugs cause relapses in schizophrenic patients in doses much lower than those needed to produce psychosis in normal persons. On the other hand, DA antagonists such as neuroleptics (DA receptor blockers) produce a pronounced improvement or remission of schizophrenic symptoms, and alpha-methyl-para-tyrosine (a DA synthesis blocker) has been reported to potentiate the clinical efficacy of neuroleptics.

Disulfiram Is a DA Agonist

Disulfiram is an inhibitor of dopamine-beta-hydroxylase (DBH), an enzyme that catalyzes the metabolism of DA to norepinephrine (NE).[3] By inhibiting the metabolic pathway from DA to NE in the central nervous system, disulfiram results in an increase of DA concentrations. Therefore, disulfiram is a DA agonist, and is likely to exacerbate preexisting or latent psychosis, similar to amphetamine, methylphenidate and L-dopa.

DA and Affective Psychosis

Increased brain DA is highly correlated with psychomotor activity in animals, and L-dopa has been shown to produce episodes of hypomania and mania in most patients with bipolar affective psychosis.[4] It is possible, therefore, that disulfiram can uncover a preexisting or latent hypomania or mania.

Alcoholism, Affective Psychosis and Schizophrenia

Alcoholism was shown to occur more frequently in the first degree relatives of patients with manic-depressive psychosis, schizophrenia and al-

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